Low Blood Pressure Is Associated With Greater Risk for Cardiovascular Events in Treated Adults With and Without Apparent Treatment-Resistant Hypertension

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Apparent treatment-resistant hypertension (aTRH) may confound the reported relationship between low blood pressure (BP) and increased cardiovascular disease (CVD) in treated hypertensive patients. Incident CVD was assessed in treated hypertensive patients with and without aTRH (BP ≥140 and/or ≥90 mm Hg on ≥3 medications or <140/<90 mm Hg on ≥4 BP medications) at three BP levels: 1: <120 and/or <70 mm Hg and <140/<90 mm Hg; 2: 120–139/70–89 mm Hg; and 3: ≥140 and/or ≥90 mm Hg. Electronic health data were matched to emergency and hospital claims for incident CVD in 118 356 treated hypertensive patients. In adults with and without aTRH, respectively, CVD was greater in level 1 versus level 2 (multivariable hazard ratio, 1.88 [95% confidence interval [CI], 1.70–2.07]; 1.71 [95% CI, 1.59–1.84]), intermediate in level 1 versus level 3 (hazard ratio, 1.32 [95% CI, 1.21–1.44]; 0.99, [95% CI, 0.92–1.07]), and lowest in level 2 versus level 3 (hazard ratio, 0.70 [95% CI, 0.65–0.76]; 0.58, [95% CI, 0.54–0.62]). Low treated BP was associated with more CVD than less stringent BP control irrespective of aTRH. *J Clin Hypertens* 2017;19:241–249.

Twenty-three reports from 1987 to 2007 established a J-curve relationship in which coronary heart disease (CHD) increased with diastolic blood pressure (DBP) values below a given threshold.[1] Four studies that refuted the J curve were re-analyzed and confirmed a J-curve relationship in patients with coronary artery disease. Eleven reports identified a J curve with low DBP and stroke, and seven found a relationship with total mortality.[1] DBP below which the risk for adverse outcomes increased varied from <70 to <100 mm Hg.

A J-curve relationship was also reported for systolic blood pressure (SBP) and DBP and either CHD, composite cardiovascular (CV) disease (CVD) events, or total mortality in adults with vascular disease.[2–5] Threshold blood pressure (BP) values below which CVD outcomes increased included <110–120/<60–70 mm Hg,[5] <110/70 mm Hg,[4] and <143/<82 mm Hg.[5] The J curve for SBP and DBP also extended to patients with treated hypertension and chronic kidney disease (CKD).[6,7] In patients with and without known vascular disease, CHD risk rose and stroke risk fell with treated SBP <120 mm Hg.[8] The Veterans Affairs Diabetes Trial reported that DBP <70 mm Hg was linked with CVD and amplified when SBP was ≥140 mm Hg.[9]

Two prospective studies reported benefit of an SBP goal <120 mm Hg vs <140 mm Hg in treated hypertensive patients. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[10] documented that stroke but not CHD or overall CV events (CVD) were reduced. The Systolic Blood Pressure Intervention Trial (SPRINT)[11] reported that the primary outcome of CHD, stroke, heart failure, and CV death was significantly reduced, as were total and CV death, with an SBP target of <120 mm Hg vs <140 mm Hg. Thus, the SPRINT results appear to refute prior observational studies.

However, SPRINT used automated office BP measurements after patients rested alone in the examination room for 5 minutes.[12] Prior research has shown that this protocol has led to SBP values 6.9 mm Hg lower than mean daytime values on ambulatory BP monitoring (ABPM).[13] Automated office SBP values in SPRINT were also 6.9 mm Hg lower than daytime ambulatory SBP in the intensive treatment group.[12] Mean daytime ambulatory SBP with SPRINT intensive treatment was likely closer to 128.4 mm Hg than the 12.1.5 mm Hg automated office value. Consequently, it is not clear whether SPRINT eliminates concerns of a J curve reported in numerous observational studies.

Treatment-resistant hypertension (TRH) is a potentially important confounding variable. In the Treating to New Targets (TNT) study,[14] patients with controlled and uncontrolled apparent TRH (aTHR) had a similar and greater risk for incident CVD than uncontrolled patients without aTRH. aTRH is used when one or more of the following are unknown: medication dose, adherence, or out-of-office BP.[15] Several other studies found that adults with aTRH, including those with controlled aTRH, were at greater risk for one or more CVD event or death than patients without aTRH.[16–18]

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These observations raise the possibility that less benefit of hypertension control in adults with aTRH[14,16–18] could reflect a larger J-curve effect. Thus, we reanalyzed our study data[18] to assess the relationship of low BP to CHD, stroke, and heart failure combined and separately in adults with and without aTRH. Low BP was defined as <120 mm Hg systolic and/or <70 mm Hg diastolic and <140/<90 mm Hg to avoid compounding the effect of diastolic BP <70 mm Hg on incident CVD when combined with SBP ≥140 mm Hg.[9] Our definitions of "low" (<120 and/or <70 mm Hg and <140/<90 mm Hg) and "usual" (120–139/70–89 mm Hg) BP control limit the range of pulse pressure (PP) in these two groups. However, CVD could partially reflect greater PP rather than only absolute SBP and DBP values.[19] Thus, the impact of PP on outcomes was examined in patients with and without aTRH. Since the impact of low treated BP may be different in patients with CKD, the relationship of low treated BP to CVD outcomes was assessed in this group.[6,7]

METHODS

The study was approved by the Office of Research Integrity at the University of South Carolina School of Medicine-Greenville. Electronic health record systems (EHRS) data from 2006–2012 were obtained from 187 clinical sites in the Care Coordination Institute quality improvement network.[18] Data were obtained under a signed Business Associate Agreement for quality improvement, which included permission to use deidentified data for research.

Inclusion and exclusion criteria

As reported,[18] adults 18 years and older with a diagnosis of hypertension, two or more clinical visits with a valid BP measurement in calendar years 2008–2012, and at least one prescription medication for any disease state were eligible. Valid BP values included systolic BP 60 mm Hg to 300 mm Hg, diastolic 40 mm Hg to 200 mm Hg, and systolic greater than diastolic BP. Exclusion criteria included: (1) CVD on a billing claim prior to 2008 or prior to first appearance in the EHRS of a participating clinic, (2) estimated glomerular filtration rate <30 mL/1.73 m^2/min, or (3) *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 403 (specifically 403.01, 403.11, 403.91), 585 (585.5-585.9), 586, active drug or alcohol abuse (*ICD-9* 303, 303.9X, 304.XX), major psychiatric illness (*ICD-9* 295.XX, 296.3, 297.X, 298.X), and malignancy (*ICD-9* 140–209). Hypertensive patients in this study were required to have at least one match to all payer Universal Billing 92/04 claims database at the Division of Health Statistics, South Carolina Revenue and Fiscal Affairs Office as described.[18]

Operational definitions

BP was defined by mean values from all clinic visits between first entry in the database to: (1) the time of but not including the day of an incident CVD event, or (2) the last entry during the study period for individuals without an event.[18]

PP (systolic BP–diastolic BP) <60 mm Hg was defined as "normal," 60–69 mm Hg as intermediate, and ≥70 mm Hg as high.[19,20]

Controlled hypertension with low BP, ie, tightly controlled hypertension, was defined as SBP <120 mm Hg and/or DBP <70 mm Hg and <140/<90 mm Hg, ie, excluded isolated systolic or diastolic hypertension. Controlled hypertension, ie, usual control hypertension, was defined as SBP 120–139 mm Hg and DBP 70–89 mm Hg. Uncontrolled hypertension included SBP ≥140 mm Hg and/or DBP ≥90 mm Hg.

aTRH was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg while prescribed three or more different classes of BP medications or <140/<90 mm Hg while prescribed four or more different classes of BP medications.[14,21] For this report, the mean number of antihypertensive medications was determined from an average of visits included in the calculation of BP. An absolute diuretic requirement was not included in the aTRH[21] definition and was not required for inclusion in our aTRH population. Visit-weighted means for BP and medication number rather than time-varying covariates were selected, since there was wide intraindividual variation in visit frequency.

Definition of outcomes

The primary outcome, incident CVD, was a composite of first emergency department or hospital admission for myocardial infarction, unstable angina, ischemic or hemorrhagic stroke, or chronic heart failure (CHF). Secondary outcomes were defined by the first occurrence of the components of the primary outcome. When an emergency department admission was followed by hospital admission, only the latter was counted as an outcome. Events occurring after a primary outcome during the study were also included in secondary outcomes. Incident CVD was defined by primary diagnoses on claims, which included *ICD-9* codes for coronary heart disease (CHD; myocardial infarction [410], unstable angina [411.1, 411.8]), CHF (428.0–428.9), and stroke (431 [hemorrhagic], 433–434 [nonhemorrhagic]).[18] Claims data did not include patient vital status. Death files were unavailable for analysis.

Data reporting and analysis

Baseline descriptive data are presented as mean and two standard errors of the mean, given the comparatively large numbers of patients and small values for one standard error. Data analyses were conducted with SAS software package (SAS version 9.03, Cary, NC). Descriptive statistics for group comparisons included t tests for continuous variables and chi-square for proportions. Given the large sample size, small and relatively minor clinical differences between groups were statistically significant.

The relationship between the dependent variable, ie, incident CVD, and various risk factors or independent variables was examined as a function of time using survival analysis. Variables with bivariate association *P* values ≤.20 were included in the multivariable model. Multicolinearity among covariates was evaluated using deviations of regression coefficients and their standard errors in the fitted univariate and multivariate models,[22,23] and none was detected. Covariates were entered simultaneously into the model. Age-adjusted Kaplan-Meier CV event-free survival curves were generated. A log-rank test was used to test the homogeneity of survival curves across racial strata.[22,23] *P* values <.05 were considered significant.

Cox proportional hazards regression was used to estimate effects of hypertension control on the incident CVD, while controlling for age, sex, race, statin use, diabetes mellitus, CKD, and aTRH. Secondary outcomes included stroke, CHD, and CHF separately and were not limited to the initial event only. Low-density lipoprotein (LDL-C) and smoking status were not included in the hazard regression analysis given >50% missing data for both. Multivariable hazards regressions analyses were conducted to assess the effect of: (1) PP on composite CVD events in patients with and without aTRH, and (2) low (L; <120 mm Hg SBP and/or <70 mm Hg DBP), intermediate (I; 120–139/70–89 mm Hg), and high (H; ≥140 mm Hg and/or ≥90 mm Hg) treated BP on composite CVD outcomes in patients with and without stage 3 CKD.

The proportional hazard assumption was tested with the goodness-of-fit chi-square test, which compares observed and expected survival probabilities, and by graphical means using log-log Kaplan-Meier curves.[23] Proportional hazards assumptions were met for each treated group. The heterogeneity of the stratum-specific hazard ratios (HRs) between SBP and incident CVD across the various stages of DBP as proposed by Breslow-Day[24] for analysis of cohort data was used. Adjusted HRs and 95% confidence intervals (CIs) are reported. CIs not overlapping 1.00 (line of identity) within group were defined as statistically significant, as were nonoverlapping 95% CIs for between-group comparisons.

RESULTS

The process for excluding patients and deriving the study sample is depicted in Figure 1. There were 118,356 patients in the analysis with 460,599 years of observation, for a mean observation period of 3.9 years.

Descriptive data for hypertensive patients subdivided by the three BP levels and number of antihypertensive medications are provided in Table I. Comparisons across groups by control status were conducted separately for patients with and without aTRH. For patients without aTRH, the low BP (<120 mm Hg and/or <70 mm Hg [L]) group was youngest and had the lowest percentage of men and the highest percentage of white patients. The L subset had the lowest body mass index (BMI) and the highest percentage of lean individuals. The uncontrolled (≥140 mm Hg and/or ≥90 mm Hg

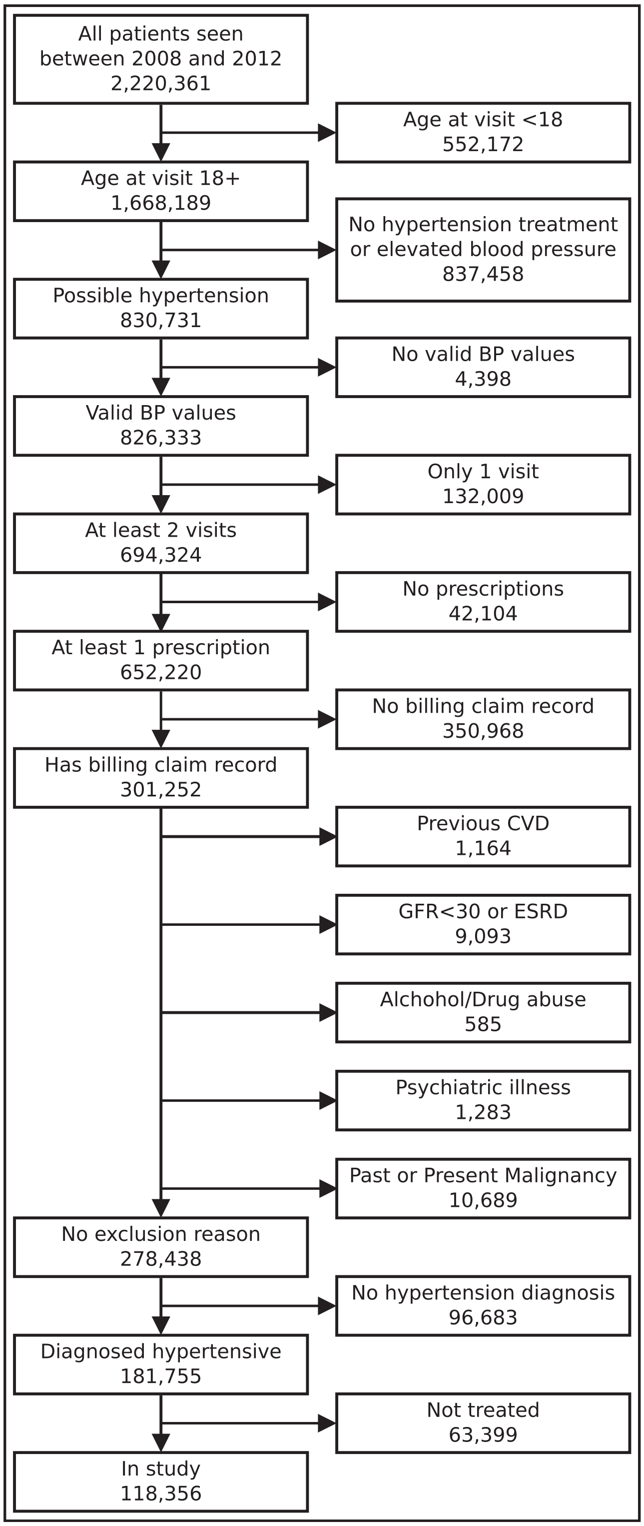

FIGURE 1. Process for derivation of study sample. BP indicates blood pressure; CVD, cardiovascular disease; GFR, glomerular filtration rate; ESRD, end-stage renal disease.

TABLE I. Characteristics of Hypertensive Adults by BP Control Status and Number of BP Medications

BP Group Variable	BP ≥140 and/or ≥90 mm Hg (Uncontrolled)		BP 120–139/70–89 mm Hg (Usual Control)		BP <120 and/or <70 and <140/<90 mm Hg (Tight Control)	
BP Medications, No.	1–2	≥3	1–3	≥4	1–3	≥4
No. (%)	18,329 (31.7)	23,057 (39.9)	41,043 (46.2)	12,320 (13.9)	18,305(52.0)	5302 (15.1)
Age, y	54.6±14.9[a,b]	58.1±15.3[a]	55.0±14.5[b,c]	60.8±14.3[c]	54.4±16.8[b]	64.0±16.3[d]
Male, %	45.1[b]	43.4[a]	43.9[b,c]	47.3[c]	40.7[b,d]	52.8[d]
White race, %	65.1[a,b]	51.6[a,b]	67.5[c]	61.4[c]	73.1[d]	74.5[d]
Black race, %	32.8[a,b]	46.7[a]	29.7[b,c]	36.1[c]	23.2[d]	22.5[d]
Other race, %	1.8[b]	1.4	2.1[b,c]	1.5	2.6[b,d]	1.6
Unknown race, %	0.3[a]	0.3[a]	0.7[b,c]	1.0[c]	1.1[d]	1.5[d]
BMI, kg/m^2	31.7±10.1[a,b]	32.2±10.1	31.3±9.6[b,c]	32.0±9.6[c]	29.5±9.9[d]	30.3±9.0[d]
<25, %	27.6[a,b]	25.9[a]	26.0[c]	23.0[c]	35.7[b,d]	30.2[d]
>30, %	47.2[b]	50.1	46.9[b,c]	51.4[c]	36.7[b,d]	42.1[d]
Visits, No. per y	3.3±2.5[a,b]	3.9±2.9[a]	3.7±2.6[b]	4.1±2.8	3.7±3.1[b,d]	4.0±3.1
SBP, last visit	144±19[a,b]	146±20[a]	129±13[b,c]	130±14[c]	118±15[b,d]	122±16[d]
DBP, last visit	82±12[a,b]	81±13[a]	78±9[b,c]	77±9[c]	68±10[b,d]	67±10[d]
SBP, all visits	149±11[a,b]	151±12[a]	130±5[b,c]	131±5[c]	117±10[b,d]	122±10[d]
DBP, all visits	85±10[a,b]	84±10[a]	79±5[b,c]	78±5[c]	68±6[b,d]	67±6[d]
LDL-C, mg/dL	107±36[a,b]	105±38[a]	104±35[b,c]	99±36[c]	98±35[b,d]	90±34[d]
Statin, %	47.9[a,b]	59.5[a]	53.3[b,c]	68.2	45.3[b,d]	70.6[d]
DM, %	26.0[b]	38.3	27.1[b]	39.7[c]	26.0[b]	45.8[d]
CKD, %	4.6[a,b]	7.5	3.9[b,c]	7.2[c]	6.1[b,d]	12.3[d]
Cigarettes, %	4.0[a]	3.6[a]	5.1[c]	4.6	4.1	3.9
10-year CHD						
>20%,	37.6[a,b]	48.4[a]	32.8[b]	46.5[c]	31.7[b,d]	53.2[d]
10%–20%	21.1[a,b]	18.8	18.2[c]	18.8	14.4[b,d]	17.1
<10%	41.3[a,b]	32.8[a]	49.0[b,c]	34.7[c]	53.9[b,d]	29.7[d]

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure. Data are presented as mean±standard deviation or percentage.

[a]*P*<.01 for uncontrolled vs usual control patients without apparent treatment-resistant hypertension (aTRH) or with aTRH (1–2 vs 1–3 and ≥3 vs ≥4 BP medications).

[b]For without vs with aTRH within the uncontrolled (1-2 vs 3 or more BP meds), controlled and tightly controlled groups (1-3 vs 4 or more BP meds).

[c]*P*<.01 for usual control vs tight control BP comparing columns with the same BP medication numbers.

[d]*P*<.01 for tight control vs uncontrolled BP (1–3 vs 1–2 and ≥4 vs ≥3 BP medications).

[H]) group had the fewest annual visits and the highest values for SBP and DBP as well as LDL-C. The L group had the lowest percentage of patients taking statins but had the highest percentage of patients with CKD and 10-year CHD risk <10%. The H group had the highest percentage of patients with 10-year CHD risk >20%.

For patients with aTRH, the L group was the oldest and the H group was the youngest. The H group had the highest and the L group had the lowest percentage of black adults. BMI was lowest in the L group, whereas visit frequency was the highest. BP values were consistent with group assignment. The H aTRH group had the highest LDL-C values and the lowest percentage of patients taking statin, while the reverse was true of the L group. The L group also had the highest percentage of patients with diabetes mellitus and CKD. Ten-year CHD risk was greatest in in the L group and lowest in the I group with BP 120–139/70–89 mm Hg.

Patients with and without aTRH were compared within BP control categories. In all three BP groups, age and annual visit number were greater in those with aTRH than those without aTRH. In the I and H groups, the percentage of white patients was lower and black patients was higher in the subset with aTRH—a difference not seen in the L group. The proportion of men was higher in the L and I groups with aTRH, a difference not seen in the H group. Across BP control groups, the subset with aTRH had fewer lean and more obese adults, more annual healthcare visits, and higher SBP and DBP. LDL-C values and percentage with diabetes mellitus, CKD, and 10-year CHD risk >20% were also higher in those with than without aTRH across BP groups.

The number of medications and the classes of antihypertensive medications prescribed in patients with and without aTRH at the three levels of treated BP are provided in Table II. As expected, the number of medications and percentages on various classes of antihypertensive medications were greater in those with than those without aTRH. The number of patient years

TABLE II. Antihypertensive Medication Classes Prescribed By Hypertension Control and aTRH Status

BP Group Variable	BP ≥140 and/or ≥90 mm Hg (Uncontrolled)		BP 120–139/70–89 mm Hg (Usual Control)		BP <120 and/or <70 and <140/<90 mm Hg (Tight Control)	
BP Medications, No.	1–2	≥3	1–3	≥4	1–3	≥4
No. (%)	18,329 (31.7)	23,057 (39.9)	41,043 (46.2)	12,320 (13.9)	18,305 (52.0)	5302 (15.1)
BP medications, No.	1.5±0.5	4.2±1.4	1.9±0.8	4.8±1.0	1.9±0.8	4.9±1.0
ACE inhibitor, %	37.2	60.6	40.4	64.2	43.3	66.2
ARB, %	18.0	40.4	19.6	42.5	15.8	39.5
DRI, %	0.7	9.2	2.3	11.3	2.6	11.0
β-Blocker, %	25.6	49.9	27.1	57.6	33.7	66.8
β,α-Blocker, %	1.0	8.1	2.6	11.1	2.9	10.8
dCCB, %	18.1	55.4	17.0	60.0	14.2	53.8
ndCCB, %	4.7	18.8	7.3	24.9	9.0	26.6
Diuretic, %	36.7	82.2	46.1	90.3	40.0	91.3
Thiazide, %	29.5	68.3	37.7	74.8	25.0	63.8
Loop, %	6.7	23.6	9.9	30.4	14.7	43.7
Aldo ant, %	0	6.2	2.0	9.9	2.5	9.7
K^+-sparing, %	3.9	17.6	7.8	24.6	10.6	27.0
α_1-Blocker, %	2.9	14.5	5.5	20.0	7.2	24.7
α_2-Agonist, %	3.1	15.4	4.0	15.6	6.8	13.4
Sympatholytic, %	0.1	1.9	0.3	2.1	0.3	2.6
Vasodilator, %	0.6	9.8	2.2	11.8	2.9	12.3

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; aTRH, apparent treatment-resistant hypertension; BP, blood pressure; DRI, direct renin inhibitor; dCCB, dihyrdropyridine calcium channel blocker; ndCCB, nondihydropyridine calcium channel blocker; K^+-sparing, potassium-sparing diuretic (amiloride, triamterene); Aldo ant, aldosterone antagonist (spironolactone, eplerenone); sympatholytics (excludes α_2-receptor agonists, eg, clonidine, guanfacine, and guanabenz, and includes reserpine, guanethidine, and guanadrel).

and primary and secondary CVD outcomes per 1000 patient years for the three levels of treated BP in patients with and without aTRH are shown in Table III.

Age-adjusted CVD-free survival is depicted in Figure 2 for six groups subdivided by BP level and aTRH status. Adults with tightly controlled hypertension with aTRH had the lowest CVD-free survival, whereas adults without aTRH and usual BP control had the fewest events. Three groups had similar CVD-free survival including uncontrolled and tightly controlled patients without aTRH and those with controlled BP with aTRH. Patients with uncontrolled TRH had more age-adjusted CVD than the three groups but fewer than patients with tight aTRH control.

The relationship of independent variables to incident CVD in multivariable hazard regressions analysis is provided in Table IV. Increasing age, diabetes, CKD, and statin use were associated with greater incident CVD risk, whereas female sex and black race were associated with lower risk, when accounting for BP group and aTRH status.

Multivariable hazards ratios for CVD by level of BP and aTRH status are provided in Figure 3. In adults without aTRH, CVD risk was higher in the L than the I group, similar in the L and H groups, and lower in the I than the H group. Among adults with aTRH, incident CVD was higher in the L vs both I and H groups. Incident CVD risk was lower in the I than the H group.

The impact of PP in patients with and without aTRH on the primary composite CVD outcome is depicted in Figure S1. The adverse effects of intermediate and high PPs were greater in treated hypertensive patients without aTRH than those with aTRH. The effect of the three levels of hypertension control on the primary CVD outcome in patients with and without stage 3 CKD is also shown in Figure S1. In hypertensive adults with stage 3 CKD, the L group had fewer events than the H group, unlike patients without CKD. Moreover, the adverse effect of L vs I level BP appeared less deleterious in patients with CKD.

DISCUSSION

In this observational study, incident CVD risk was greater in treated patients with tight than usual BP control, ie, SBP <120 mm Hg and/or DBP <70 mm Hg and <140/<90 mm Hg vs 120–139/70–89 mm Hg. Our principal finding is consistent with several studies suggesting a J- or U-shaped relationship between BP and CVD outcomes in patients treated for hypertension.[1,4-8] The greater CVD risk with tight than usual BP control included patients with and without aTRH. In patients with aTRH, the tightly controlled group also had greater CVD risk than the uncontrolled group, whereas these two groups had similar CVD risk in adults without aTRH.

The risk for incident CVD was lowest in treated patients with and without aTRH who had BP controlled to 120–139/70–89 mm Hg. The benefit of usual control

TABLE III. Unadjusted Primary and Secondary Outcomes By BP Control Status and Medication Number

BP Controlled Status	Uncontrolled (57,749 [31.8%])		Controlled Normal BP (88,808 [48.9%])		Controlled Low BP (35,198 [19.4%])	
BP medication, No.	1–2	≥3	1–3	≥4	1–3	≥4
No. (%)	18,329 (31.7)	23,057 (39.9)	41 043 (46.2)	12,320 (13.9)	18,305 (52.0)	5302 (15.1)
Patient-years	72,569	89,438	164,851	48 720	66,449	18,576
Primary outcome, No./1000 patient-years	22.8	34.4	13.7	27.6	24.2	62.6
Secondary outcomes, No./1000 patient-years						
Stroke, hemorrhagic	1.4	1.8	0.6	1.2	1.3	1.9
Stroke, ischemic	4.8	7.0	2.2	4.1	3.5	8.3
CHD, unstable angina	4.0	6.0	3.1	6.6	4.6	12.9
CHD, myocardial infarction	5.3	7.3	3.2	5.2	5.2	11.3
Congestive heart failure	13.1	23.3	8.3	19.9	17.3	50.8

Abbreviations: BP, blood pressure; CHD, coronary heart disease.

TABLE IV. Multivariable Hazards Regression Analysis of Variables Associated With Composite Incident Cardiovascular Events (CVD)[a]

Variable	Reference	Hazard Ratio	95% CI
Age, y		1.018	1.017–1.020
Female sex	Male	0.77	0.74–0.80
Black race	White	0.90	0.86–0.94
Diabetes mellitus	No diabetes	1.53	1.46–1.60
CKD	No CKD	2.34	2.16–2.54
Statin	No statin	1.48	1.41–1.56

Abbreviations: CI, confidence interval; CKD indicates chronic kidney disease; CVD, cardiovascular disease.

[a]Variables without interactions.

vs uncontrolled hypertension was lower in adults with aTRH than those without aTRH (Figure 2). We reported that hypertension control, which included both the tight and usual control groups in this report, afforded less benefit from incident CVD in patients with aTRH, particularly for chronic heart failure (CHF).[18]

CVD risk associated with tightly controlled vs uncontrolled hypertension varied by CVD outcome and aTRH status (Figure 3). For the composite CVD outcome, tight control was associated with worse outcomes than usual control in patients with but not in patients without aTRH. For stroke, tight hypertension control was associated with fewer events than uncontrolled hypertension in patients with and without aTRH. For CHD, tight control was better than uncontrolled hypertension in patients without but not in patients with aTRH. For CHF, tight control was associated with more events than usual control in patients with and without aTRH.

Several studies documented a relationship between tight BP control and CHD. The association is generally explained by inadequate coronary perfusion during diastole to meet myocardial oxygen demands. Eleven studies reported a relationship between tight BP control and stroke, although other reports indicate fewer stroke events in hypertensive patients with BP controlled to <120 mm Hg systolic vs less stringent control.[1,2,8] Ischemic stroke risk has been linked to low or rapid declines in nocturnal BP in some[25,26] but not all reports.[27] Thus, among at-risk adults with tight BP, attention to nocturnal values may identify a subset of patients at greater risk.

To our knowledge, this is the first study to assess the relationship between tight BP control and CVD in the presence or absence of aTRH. We previously reported that BP control provided less protection against CVD in patients with than those without aTRH,[18] which is consistent with earlier publications.[14,16,17] One potential explanation was the presence of a greater adverse effect of tightly controlled hypertension in patients with aTRH than in patients without aTRH. However, in the present study, the multivariable hazards ratio for tight vs usual BP control and CVD was similar in patients with and without aTRH (Figure 2).

A critical issue in understanding the clinical implications of this observation is whether the tight BP control is causal or reflects confounders not included in the multivariable hazards regression model. For example, patients with TRH have more severe insulin resistance,[28] which, in turn, is associated with greater disorders of carbohydrate and lipid metabolism, neurohormonal activation, endothelial function, and CV structure and function and imbalance of fibrinolytic and thrombogenic factors.[29,30] While diabetes mellitus was included in the hazards regression analysis, several other risk factors associated with insulin resistance were not. In fact, lipid profile data and cigarette smoking status were obtainable from the EHRS in fewer than half of the patients. Consequently, we did not include these risk factors in the multivariable analysis.

Patient adherence is another potential confounder in the association of BP level with outcomes. Better adherence, including adherence with a placebo, is associated with reduced CVD.[31,32] Suboptimal adherence is well documented in patients with uncontrolled hypertension, especially those with uncontrolled

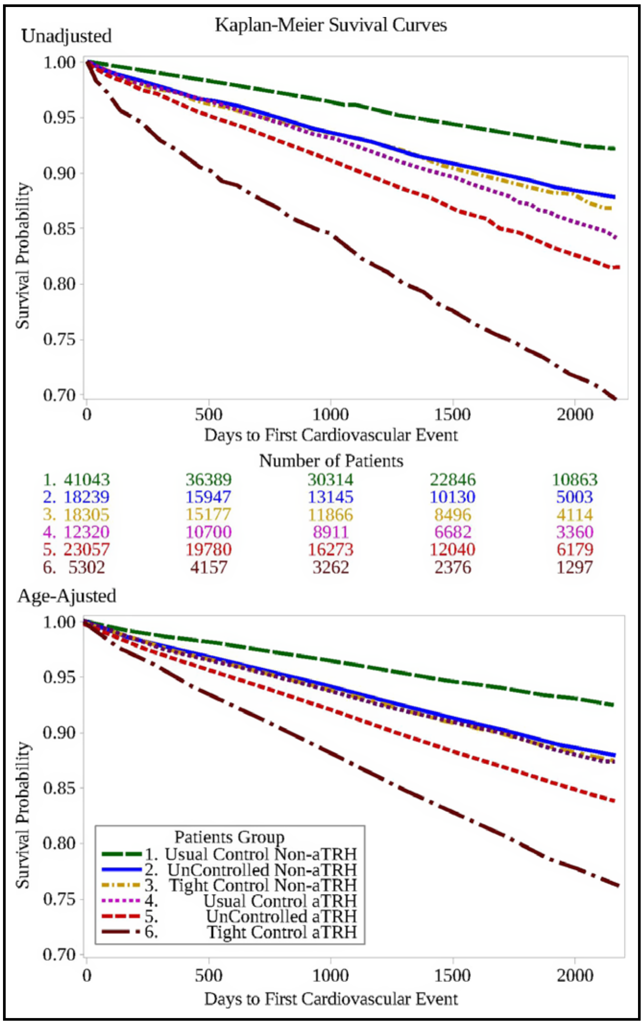

FIGURE 2. Cardiovascular event-free survival by blood pressure level and apparent treatment-resistant hypertension (aTRH) status (unadjusted).

treatment-resistant hypertension.[33] Nevertheless, the aTRH group with tightly controlled hypertension, which is likely to be compliant with their antihypertensive medications, had worse outcomes than those with uncontrolled hypertension (Figures 1 and 2). The group with tightly controlled hypertension not only had lower BP but were also more likely to have a statin prescription and to have lower values of LDL cholesterol. These data provide indirect evidence suggesting that the tightly controlled group was adherent with prescribed medications. Thus, low adherence levels are an unlikely explanation for worse CVD outcomes in the tightly controlled aTRH group. Patients with aTRH, as expected, were more likely to receive all classes of antihypertensive medications. No major differences were apparent between patients with usual and tight hypertension control that could account for the markedly different clinical CVD outcomes (Table II).

PP is a potential confounder of the relationship of BP control status to CVD outcomes. PP assumes increasing importance as a determinant of CVD outcomes with increasing age, and patients with aTRH were generally older than those without aTRH.[19,20,34] However, differences in PP appeared to have less effect on CVD outcomes in patients with than those without aTRH (Figure S1). The presence or absence of CKD may also modify the effect of tightly controlled hypertension on outcomes.[6,7] While our study included only patients with stage 3 CKD, low treated BP was associated with lower CVD among patients with but not those without stage 3 CKD.

Limitations

Individuals with a documented hospital or emergency department claim for CVD prior to 2008 and to their first documented clinical visit were excluded. However, patients with tightly controlled hypertension may have more subclinical heart and vascular disease, which magnified their CVD risk. The tightly controlled subset of patients with aTRH were the oldest and had the highest prevalence of diabetes mellitus and CKD. This group would be expected to have more subclinical heart and vascular disease, which would place them at greater risk for CVD events. Nonetheless, the tightly controlled group of patients without aTRH were not older nor did they have a greater prevalence of diabetes or CKD than patients without aTRH with either usual control or uncontrolled hypertension. Yet, among patients without aTRH, the tightly controlled group had more CVD than the group with higher but controlled BP. Of note, post hoc analyses of completed trials suggest that the subset of patients with tightly controlled hypertension had a more adverse risk factor profile, which may explain adverse outcomes rather than low treated BP.[35]

Additional study limitations include its observational design rather than a prospective randomized investigation of different levels of BP control, eg, ACCORD or SPRINT.[10,11] Data on LDL cholesterol and smoking status were missing for a large proportion of patients. The definition of tightly controlled hypertension as SBP <120 mm Hg and/or DBP <70 mm Hg is consistent with many but not all reports cited,[1–9] ie, arbitrary. The analysis was based on diagnoses in medical claims and not an end points committee. Fatal and nonfatal CVD events could not be distinguished as mortality data were unavailable. Although the mean observation period was 3.9 years, it was not possible to identify untreated BP or BP at the time of initial treatment in the majority of patients, as previously reported.[36] Despite these limitations, the analysis included a large number of patients (118,356) and observation years (460,599). While the tightly controlled aTRH group was the smallest, it included 5302 patients with 18,576 observation years. The negative association of black race and positive association of statins with CVD were previously noted.[18]

CONCLUSIONS

Patients with aTRH are at greater CVD risk than those without aTRH. In patients with and without aTRH and controlled hypertension, the subset with BP <120 mm Hg and/or diastolic BP <70 had more strokes, CHD, and CHF than those with BP 120–139/70–89 mm Hg. Among adults with aTRH, the tightly controlled subset also had more CVD events than those with uncontrolled hypertension. Our analysis cannot establish a cause-and-effect relationship between tight BP control and adverse outcomes. Clinicians should consider the possibility that their patients with tightly controlled hypertension are at greater risk for CVD. Detection of subclinical heart and vascular disease in these individuals may identify the subset at greatest risk for whom complementary risk reduction measures may be appropriate.

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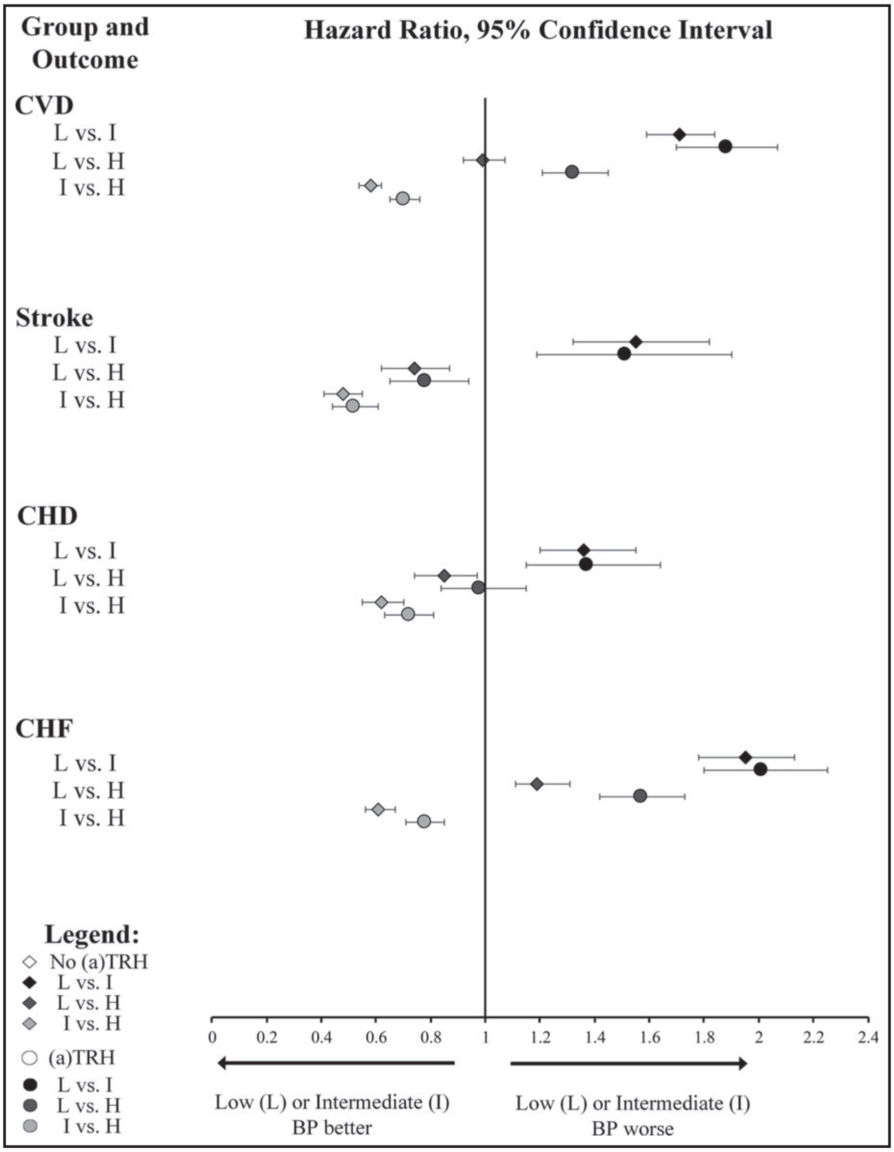

FIGURE 3. Cardiovascular outcomes by resistant hypertension and blood pressure (BP) control status. CVD indicates cardiovascular disease; CHD, coronary heart disease; CHF, congestive heart failure; (a)TRH, apparent treatment-resistant hypertension. L, BP <120 systolic and/or <70 diastolic and <140/<90; I, BP 120-139/70-89; H, systolic 140 or higher and/or diastolic 90 or higher.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. The effect of pulse pressure (upper panel) and Stage 3 CKD (lower panel) on composite cardiovascular (CV) events is provided for patients without (open symbols) and with (filled symbols) aTRH. In the upper panel, intermediate (60–69 mm Hg) and high (≥70 mm Hg) as compared to normal pulse pressure (<60 mm Hg) were associated with more CV events in patients with and without aTRH but the adverse was less in those with aTRH. In the lower panel, low (L, <120 systolic or <70 diastolic and <140/<90) was associated with more CV events than intermediate BP (I, 120–139/80–89 mm Hg) in patients with and without Stage 3 CKD. The adverse effect of low BP was less in patients with CKD. Low as compared to high (H, >140 systolic and/or >90 diastolic) was associated with fewer CV events in patients with CKD but not in patients without CKD. I vs. H BP was associated with a similar reduction of CV events in both groups.